REMARKS

Claims 74-142 were pending in the application. Claims 83, 84-88, 91, 93, 95, 97, 99-103, 106, 108, 110, 112, 120, 122-127, 129-133, 135, 137-140 have been amended. Claims 90, 92, 94, 96, 98, 105, 107, 109, 111, 113, 128, 134, 136 have been cancelled. Accordingly, claims 74-89, 91, 93, 95, 97, 99-104, 106, 108, 110, 112, 114-127, 129-133, 135, and 137-142 are currently pending in the application upon entry of this Amendment.

Claims 88, 90, 91, 93, 95, 97, 101, 103, 106, 108, 110, 112, 122, and 139 have been amended for typographical errors and to correct formalities. Support for the amendment to claims 84-88, 99-103, 123-127, 129-133 can be found throughout the specification, including at least at page 29, line 28 to page 32, line 35. Support for the amendment to claims 83 and 122 can be found in the specification at least at page 30, line 32. Support for the amendment of claims 135 and 137-140 can be found in previously examined claim 136 and throughout the specification, including at least at page 29, line 28 to page 31, line 12. Claims 88, 91, 93, 95, 97, 101, 103, 106, 108, 110, 112, 120, 122, and 139 have been amended for formalities and to correct inadvertent typographical errors.

No new matter has been added. The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Objection of Claims 88, 101, 103, 120 and 139 Based on Informalities

The Examiner has objected to claims 88, 101, 103, 120 and 139 based on informalities. Applicant has amended claims 88, 101, 103, 120, and 139 to correct the referenced informalities.

Rejection of Claims 88, 91-98, 103, 106-113, and 122 Under 35 U.S.C § 112, Second Paragraph

The Examiner has rejected claims 88, 91-98, 103, 106-113, and 122 under 35 U.S.C. 112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

The Examiner has rejected claims 88 and 103 as being improper for containing a Markush group that does not have an "and" before the last member. Applicant has amended

claims 88 and 103 to include the word "and" before the last member of the Markush group, thus rendering the rejection moot.

The Examiner has rejected claims 88, 91, 93, 95, 97, 103, 106, 108, 110, and 112 for reciting the phrase "any one of claims" where the claim depends from only one claim. Claims 88, 91, 93, 95, 97, 103, 106, 108, 110, and 112 have each been amended to recite the word "claim," thus rendering the rejection moot.

The Examiner has rejected claim 122, because the phrase "the additional therapeutic agent" lacks antecedent basis. Applicant has amended the claim appropriately, thereby rendering the rejection moot.

In view of the amendments to claims 88, 91, 93, 95, 97, 103, 106, 108, 110, 112, and 122, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection of Claims 88, 103, 122-127, and 129-133 Under 35 U.S.C § 112, First Paragraph

The Examiner has rejected claims 88, 103, 122-127 and 129-133 under 35 U.S.C., first paragraph for failing to comply with the written description requirement because they allegedly contain new matter. The Examiner states that Applicant has "improperly extended the originally disclosed treatment method." Applicant respectfully traverses this rejection.

Claims 88, 103, 123-126 and 129-132 have been amended to specify certain types of additional therapeutic agents, *i.e.,* a cytokine suppressive anti-inflammatory drug (CSAID), a non-steroidal anti-inflammatory drug (NSAID), a second antibody, a fusion protein, and an anti-inflammatory cytokine. These claims were amended solely to expedite prosecution of the present application. Applicant reserves the right to prosecute the same or similar claims in this application or another application. With regard to the amended claims, for the reasons of record and those described below, Applicant has provided sufficient teachings in the specification such that one of ordinary skill in the art would understand that Applicant was in possession of the claimed invention, *i.e.,* administering the claimed additional therapeutic agents in combination with the claimed antibody to a human subject suffering from a disorder in which TNFα activity is detrimental.

An objective standard for determining compliance with the written description requirement under 35 US.C. §112, first paragraph, is whether the specification conveys with

reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

The subject matter of the claim need not be described literally (*i.e.*, using the same terms or in haec verba) in order for the disclosure to satisfy the written description requirement. As phrased by the court in *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 USPQ2d 1895 (Fed. Cir. 1996), "ipsis verbis disclosure is not necessary to satisfy the written description requirement of 35 U.S.C. § 112. Instead, the disclosure need only reasonable convey to persons skilled in the art that the inventor had possession of the subject matter in question." Id. at 1570.

Claim 84 is directed to a method for inhibiting human TNFα activity in a human subject suffering from a disorder in which TNFα activity is detrimental, comprising administering to the human subject an antibody and at least one additional therapeutic agent selected from the group consisting of a cytokine suppressive anti-inflammatory drug (CSAID), a non-steroidal anti-inflammatory drug (NSAID), a second antibody, a fusion protein, and an anti-inflammatory cytokine, such that human TNFα activity is inhibited, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a Kd of 1 x 10-8 M or less and a Koff rate constant of 1 x 10-3 s-1 or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard in vitro l929 assay with an IC50 of 1 x 10-7 M or less. Claim 99 is directed to a method for treating a subject suffering from a disorder in which TNFα activity is detrimental, comprising administering to the subject an antibody and at least one additional therapeutic agent selected from the group consisting of a cytokine suppressive anti-inflammatory drug (CSAID), a non-steroidal anti-inflammatory drug (NSAID), a second antibody, a fusion protein, and an anti-inflammatory cytokine, such that the disorder is treated, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a Kd of 1 x 10-8 M or less and a Koff rate constant of 1 x 10-3 s-1 or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard in vitro L929 assay with an IC50 of 1 x 10-7 M or less. In one embodiment, as described in claims 88 and 103, the second antibody is selected from the group consisting of CDP-57111/bay-10-3356, cA2, IDEC-CE9.1/SB 210396, Anti-Tac, IL-4 agonist antibody, IL-10 agonist antibody, an anti-CD4

antibody, anti-IL-1β monoclonal antibody, anti-IL-6 monoclonal antibody, anti-IL-8 antibody, anti-IL-12 antibody, and an anti-IL2R antibody. In another embodiment, as described in claims 123 and 129, the CSAID is either leflunomide or T-614. In another embodiment, as described in claims 124 and 130, the NSAID is selected from the group consisting of tenidap, naproxen, meloxicam, Diclofenac, ibuprofen, piroxicam, indomethacin, and leflunomide. In another embodiment, as described in claims 125 and 131, the anti-inflammatory cytokine is selected from the group consisting of interleukin-11, interleukin-13, IL-4, and IL-10. In another embodiment, as described in claims 126 and 132, the fusion protein is selected from the group consisting of 75 kdTNFR-IgG, 55 kdTNFR-IgG, DAB 486-IL-2, and DAB 389-IL-2.

Claim 127 is directed to a method for inhibiting human TNFα activity in a human subject suffering from a disorder in which TNFα activity is detrimental, comprising administering to the human subject an antibody and at least one additional therapeutic agent such that human TNFα activity is inhibited, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and a K_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} M or less, wherein the additional therapeutic agent is selected from a group consisting of a number of additional therapeutic agents.

Finally, claim 133 is directed to a method for treating a subject suffering from a disorder in which TNFα activity is detrimental, wherein the disorder is selected from the group consisting of periodontal disease, obesity, and radiation toxicity, comprising administering to the subject an antibody such that the disorder is treated, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a k_d of 1 x 10^{-8} m or less and a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1 x 10^{-7} m or less. In one embodiment, the isolated human antibody is administered with at least one additional therapeutic agent selected from the group consisting of agent is selected from a group consisting of a number of additional therapeutic agents.

Applicant maintains that claims 88, 103, 122-127 and 129-133 do not contain new matter relative to the original disclosure. The non-limiting examples of additional therapeutic agents

described in the specification as suitable for administration to subjects having certain disorders, *e.g.*, rheumatoid arthritis, were not meant to limit the administration of the recited therapeutic agents only to subjects having the specific disorder. Based on the teachings of the instant specification, one of ordinary skill in the art would recognize that each additional therapeutic agent described for a specific disorder could also be administered in combination with the antibody of the invention for the treatment of other disorders in which TNFα activity is detrimental. In addition to the support in the specification described in Applicant's previous response, the specification at page 29, lines 16-20 teaches examples of additional therapeutic agents which can be coadministered with the antibody of the invention, including "one or more additional antibodies that bind other targets (*e.g.*, antibodies that bind other cytokines or that bind cell surface molecules), other cytokines, soluble TNFα receptor...and/or one or more chemical agents that inhibit hTNFα production or activity." Specific examples of these types of additional therapeutic agents, *i.e.*, additional antibodies, other cytokines, soluble TNFα receptor, and chemical agents, are described at pages 29 to 32 in the specification for exemplary types of disorders in which TNFα activity is detrimental, *i.e.*, rheumatoid arthritis.

The specification teaches examples of specific types of disorders in which TNFα activity is detrimental at pages 36 to 40. The specification also teaches that said disorders may be treated with the antibody of the invention in a combination therapy using additional therapeutic agents. For example, Applicant teaches that the antibody of the invention can be coadministered for the treatment of an autoimmune disease with one or more additional therapeutic agents (see page 37, lines 21-24 of the specification). Applicant teaches that rheumatoid arthritis and multiple sclerosis are examples of autoimmune diseases (see page 37, lines 15-16 of the specification), and provides exemplary agents which can be used in combination treatment at pages 29-32. Accordingly, one of ordinary skill in the art would recognize based on the teachings of the specification that the list of additional therapeutic agents listed at pages 29 to 32 for rheumatoid arthritis and multiple sclerosis can be administered in combination with the antibody of the invention for the treatment of other types of autoimmune diseases and other disorders in which TNFα activity is detrimental.

In view of the foregoing teachings in Applicant's specification, the ordinarily skilled artisan would understand that Applicant was in possession of the claimed invention at the time of

filing. Accordingly, Applicant respectfully requests that the rejection of claims 88, 103, 122-127 and 129-133 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Rejection of Claims 83, 90, 105, 122, 124, and 130 Under 35 U.S.C. 112, First Paragraph

Claims 83, 90, 105, 122, 124, and 130 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner states the Markush group member "corticosteroids" recited in these claims is broader than what was originally disclosed as "corticosteroid anti-inflammatory drugs." Applicant respectfully traverses this rejection, however, in the interest of expediting prosecution, Applicant has amended claims 83, 90 and 122, to recite to the term "corticosteroid anti-inflammatory drug." Claims 124 and 130 have been amended and no longer recite the term "corticosteroid." Claim 105 has been cancelled. Thus, in view of the amendment to claims 83, 90, 122, 124, and 130, the rejection has been rendered moot.

Rejection of Claims Under Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 74-82 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 24-25, and 28 of U.S. Patent No. 6,090,382. Claims 74 and 83 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 24-25 of U.S. Patent No. 6,090,382 in view of Aggarwal (U.S. Patent No. 5,795,967). Claims 84-87, 89, 91, 93, 95, 97, 99-102, 104, 106, 108, 110, 112, 135, and 138-140 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7, 15, 17, 22, 36-39, 69, 87, and 93 of U.S. Patent No. 6,509,015. Claims 84-87, 89-91, 93-97, 99-102, 104-106, 108-112, 123-125, 127-131, 133-134, and 136-137 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7, 15, 17, 22, 36-39, 69, 87, and 93 of U.S. Patent No. 6,509,015 in view of Aggarwal (U.S. Patent No. 5,795,967). Claims 84-88, 91-92, 98-103, 106-107, 112-113, 126, 132, and 141-142 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-7, 36-39, and 69 of U.S. Patent No. 6,509,015. Claims 114-121 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 4-7 and 36-39 of U.S. Patent No. 6,509,015. Claims 118 and 122 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4, 36 and 69 of U.S. Patent No. 6,509,015 in view of Aggarwal (U.S. Patent No. 5,795,967).

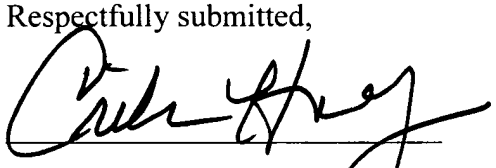
While in no way admitting that the above-mentioned claims are obvious over the cited claims of U.S. Patents 6,090,382 and 6,509,015, upon allowance of the instant application, Applicant will consider submitting a terminal disclaimer upon indication that the claims are allowable.

SUMMARY

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. It is respectfully submitted that any amendments and/or cancellations of the claims should in no way be construed as an acquiescence to the Examiner's rejections and/or objections.

If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's Attorney at (617) 227-7400.

Respectfully submitted,



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